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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. |
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| 09/207,649 | 12/08/98 | LINDQUIST S | ARCD:278 |

HM12/0804

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| EXAMINER | |
|---|---|
| TURNER, S | |
| **ART UNIT** | **PAPER NUMBER** |
| 1645 | 5 |

**DATE MAILED:** 08/04/99

**Please find below and/or attached an Office communication concerning this application or proceeding.**

**Commissioner of Patents and Trad marks**

# Office Action Summary

| Application No. | Applicant(s) |
|---|---|
| 09/207,649 | Lindquist |
| **Examiner** | **Group Art Unit** |
| Sharon L. Turner, Ph.D. | 1645 |

☒ Responsive to communication(s) filed on *3-24-99*.

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

**Disposition of Claims**

☒ Claim(s) *1-36* is/are pending in the application.

Of the above, claim(s) *23-36* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-22* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

**Application Papers**

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. § 119**

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

**Attachment(s)**

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *5*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

*--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---*

## DETAILED ACTION

### *Priority*

1. If applicant desires priority under 35 U.S.C. based upon a previously filed copending application, specific reference to the earlier filed application must be made in the instant application. This should appear as the first sentence of the specification following the title, preferably as a separate paragraph. The status of nonprovisional parent application(s) (whether patented or abandoned) should also be included. If a parent application has become a patent, the expression "now Patent No._____" should follow the filing date of the parent application. If a parent application has become abandoned, the expression "now abandoned" should follow the filing date of the parent application.

The instant application incorrectly recites priority based upon 60/069,168 filed May 8, 1998. Application 60/069,168 was filed December 9; 1997. Application 60/084,824 was filed May 8, 1998. Correction is required.

### *Information Disclosure Statement*

2. The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be

incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

3. The IDS has been considered to the extent indicated on PTO-1449. The Glover et al, 1997 reference, C29, was not considered as pages 812, 814, 816 and 818 were not provided. This reference will be timely considered when received by the Examiner. The applicant may Fax a copy of the missing pages.

***Drawings***

4. The drawings submitted with this application were declared informal by applicant. Accordingly they have not been reviewed by a draftsperson at this time. When formal drawings are submitted, the draftsperson will perform a review. Direct any inquires concerning drawing review to the Drawing Review Branch (703) 305-8404.

***Election/Restriction***

I. Claims 1-22, drawn to a method of identifying aggregation inhibitors, classified in class 536, subclass 17.5.

II. Claims 23-26, drawn to a method of identifying a therapeutic, classified in class 424, subclass 75.

5. The inventions are distinct, each from the other because of the following reasons:

6. Groups I and II are related as processes. Groups I and II differ each from the other in the structure of the molecules identified and their functional abilities. The molecules of Group I may be organic or inorganic compounds identified by the ability to inhibit aggregation. The molecules of Group II may be organic or inorganic compounds identified by the ability to provide a patient therapeutic benefit.

7. Because these inventions are distinct for the reasons given above and have acquired a separate status in the art as shown by their different classification, and recognized divergent subject matter restriction for examination purposes as indicated is proper.

8. Because these inventions are distinct for the reasons given above and the search required for each of the groups is not required for any other group, restriction for examination purposes as indicated is proper.

Applicant is advised that the reply to this requirement to be complete must include an election of the invention to be examined even though the requirement be traversed (37 CFR 1.143).

9. During a telephone conversation with Mr. Mark Wilson on 7-07-99 a provisional election was made with traverse to prosecute the invention of Group I, claims 1-22. Affirmation of this election must be made by applicant in replying to this Office action. Claims 23-36 withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

*Claim Rejections - 35 USC § 112*

10. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

11. Claim 6 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. It is unclear what is meant by an aggregate forming domain of a mammalian amyloid polypeptide.

12. Claims 3, and 12-14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. $PrP^c$ and B-amyloid are prion proteins and amyloid proteins with recognized structure. Applicants contemplate aggregate-prone amyloid proteins, to be of essentially any origin, and having the ability to aggregate under physiological conditions such as inside of a cell, page 5, lines 16-23. In addition, IDS Reference, Wickner et al teaches also teaches a definition of a prion to include any protein that indefinitely propagates an altered form of itself (without the continued presence of a special external stimulus) and is transmissible, see page 568 column 3, paragraph 4. It is unclear whether applicant wishes to consider PrP to mean a prion protein as defined by the ability to aggregate or alternatively whether PrP and B-amyloid intend to convey a certain structure. Please clarify the meaning of such terminology based upon either structure and/or function.

***Claim Rejections - 35 USC § 102 or 103***

13. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

14. Claims 1-2, 4, 6-7, 9, and 12 are rejected under 35 U.S.C. 102(b) as being anticipated by IDS Ref., Wickner et al, Science, 1994, 264:566-569. Claims 3, 5, 8-11 and 13-22 are rejected as being dependent upon these rejected claims. Claim 1 is drawn to a method of identifying a candidate substance that inhibits the aggregation of an aggregate-prone amyloid protein comprising: (a) contacting a yeast cell that expresses an aggregate-prone amyloid protein with said candidate substance under conditions effective to allow aggregated amyloid formation; and (b) determining the ability of said candidate substance to inhibit the aggregation of the aggregate-prone amyloid protein. Wickner et al teaches saccharomyces cerevisiae yeast strains which express an Ure2p protein from the Ure gene which exists in normal form, providing [ure3] nonaggregating phenotype and in prion form, providing [URE3] aggregating phenotype. Ure2p is an aggregate-prone amyloid protein based upon applicants definition, specification, page 5. Wickner et al teach the inhibition of aggregate formation (conversion to [URE3]) by steps (a) and (b) above comprising inhibition of aggregation by growth of cells on media containing guanidine HCl, see abstract, Figure 1, page 567 column 2, lines 3-10. Wickner et al therefore teach all the limitations of claim 1. Wickner et al also teach the limitations of claim 2 because the method

comprises URE3. Wickner et al teach, page 568, a (GST)-Ure2p fusion protein capable of transferring the [URE3] aggregating phenotype to *S. cerevisiae*, thus meeting the limitations of claim 4, (wherein the aggregate-prone amyloid protein is a chimeric protein). Claim 6 is anticipated by Wickner et al based upon the definition of an aggregate-prone amyloid protein, see specification page 5 as the chimeric protein, being an aggregate-prone amyloid protein, comprises an aggregate forming domain of a mammalian amyloid polypeptide. Claim 7 is anticipated by Wickner et al as the chimeric protein is operably attached to detectable marker proteins, GST and Ure2p. Wickner et al anticipate claim 9 as mutants possess the ability to utilize ureidosuccinate, Reference 8. Claim 12 is anticipated by Wickner et al as the definition of an aggregate-prone amyloid protein encompasses the chimeric protein, which aggregates and contains an aggregate forming domain of a mammalian polypeptide. The amyloid polypeptide is a prion protein and an amyloid protein, see specification, page 5. Applicants contemplate aggregate-prone amyloid proteins, to be of essentially any origin, and have the ability to aggregate under physiological conditions such as inside a cell, page 5, lines 16-23. Wickner et al, teach the definition of a prion protein to include any protein that indefinitely propagates an altered form of itself (without the continued presence of a special external stimulus) and is transmissible, see page 568 column 3, paragraph 4. Since Wickner et al teach Ure2p prion proteins and Ure2p amyloid proteins capable of aggregating, Wickner et al anticipates the limitations of claim 12.Thus Wickner et al anticipates claims 1-2, 4, 6-7, 9 and 12.

15. Claims 1-2, 4-7, and 21-22 are rejected under 35 U.S.C. 102(b) as being anticipated by Chernoff et al, Science, 1995, 268:880-884. Claims 3 and 8-20 are rejected as being dependent upon these rejected claims. Claims 1-2, 4, and 6-7 are set forth above. Chernoff et al describe a method capable of identifying Hsp104 as an inhibitor of aggregation of Sup35 in *S. cerevisiae*, claims 1-2, 6-7. Hsp104 was required for propagation of [psi+], prion formation and amyloid aggregation. However, overproduction of Hsp104 or inactivation of Hsp104 by mutation causes loss of [psi+], inhibition of prion formation and amyloid aggregation, (claim 4). See for example, Abstract, p 882 column 1 line 34 and column 2 line 6. Chernoff et al also teach, page 883 line 9, GuHCl mediated cure of [psi+], prion formation and amyloid aggregation, and that Hsp104 protein is increased about three to fivefold by growth in the presence of 5 to 10 mM GuHCl, claims 1-2 and 6-7. Claim 5 is anticipated as the chimeric protein comprises the N-terminal domain of Sup35. Claim 21 is anticipated as the aggregation is determined by the presence of a [PSI+] phenotype. Claim 22 is anticipated as the yeast cell overexpresses Hsp104. Thus, Chernoff et al anticipates claims 1-2, 4-7, and 21-22.

16. Claims 1-2, 4-7, 9, 16-18 and 21-22 are rejected under 35 U.S.C. 102(b) as being anticipated by IDS Ref., Paushkin et al, EMBO Journal, 1996, 15(12):3127-3134. Claims 3, 8, 10-15 and 19-20 are rejected as being dependent upon these rejected claims.

Paushkin et al anticipates claims 1-2, 4-7, 9 and 12, set forth above. Paushkin et al teach *S. cerevisiae* Sup35p normal and prion proteins capable of providing the [psi+] aggregating phenotype to cells. Paushkin et al teach contacting cells with N-terminally altered Sup35p

molecules unable to aggregate and provide the [psi+] phenotype (claims 1-2 and 6-7). Paushkin et al also teach contacting this cell type with plasmids overexpressing Hsp104 chaperone protein which inhibits Sup35p aggregation and the [psi+] phenotype. Paushkin et al anticipates claims 4, 16-18 and 21-22 as the aggregate prone amyloid proteins comprise Sup35 (claim 2), the aggregate proteins are Sup35 GST-chimeric proteins (claim 4, abstract), the proteins comprise at least the N-terminal domain of Sup35 (claim 5, abstract), the proteins comprise at least an aggregate forming domain of a mammalian amyloid polypeptide (claim 6, by definition, specification, page 5), the proteins are operably attached to a detectable GST marker protein (claim 7, see p 3128-9), the marker protein is a GST drug-resistance marker protein (claim 9, Materials and Methods), the aggregate-prone amyloid protein is detected by increased protease resistance of the aggregated protein (claim 16, see Figure 5), the aggregate protein is labeled with an electrochemiluminescent fluorophore (claims 17-18, see Materials and Methods), the aggregation is determined by the presence of a [PSI+] phenotype (claim 21, abstract), and the yeast cells over expresses Hsp104 (claim 22, abstract).

17. Claims 1-2, 4-11, 17-18, 20-22 are rejected under 35 U.S.C. 102(b) as being anticipated by IDS Ref., Patino et al, Science, 273:622-626, 1996. Claims 3, 12-16 and 19 are rejected as being dependent upon these rejected claims. Claims 1-2, 4-7, and 9 are set forth above. Patino et al disclose amyloid and prion aggregation of a GFP chimeric Sup35 fusion protein in yeast. Aggregation was dependent on the intracellular concentration and functional state of Hsp104 and [psi+] phenotype with Hsp104 overexpression resulting in inhibition of [psi+] and Sup35 prion

aggregation. Claim 8 is anticipated by Patino et al as the Sup35 marker protein is green fluorescent protein. Claim 9 is anticipated by Patino et al as the marker is a drug resistance protein -ade, -ura, see Figure 2. Claims 10-11 are anticipated as Patino et al teach a glucocorticoid inducible Hsp104 fusion, page 623, column 1 line 11. Claims 17-18 are anticipated by Patino as the aggregate-prone Sup35-GFP fusion is labeled as a fluorophore. Claim 20 is anticipated by Patino as the fluorophore is green fluorescent protein. Claims 21 and 22 are anticipated by Patino as the aggregates are determined by the presence of a [psi+] phenotype and the yeast cell overexpresses Hsp104. Thus claims 1-2, 4-11, 17-18 and 20-22 are anticipated by Patino et al.

18. Claims 1, 3-4, 6-7, 12-13, and 17-18 are rejected under 35 U.S.C. 102(b) as being anticipated by Hughes et al, PNAS, 93:2065-70, 1996. Claims 2, 5, 8-11, 14-16 and 20-22 are rejected as being dependent upon these rejected claims. Claim 1 is set forth above. Hughes et al teach claim 1, a yeast-two hybrid system as a method of identifying amyloid fragments which are capable of inhibiting amyloid aggregation, see abstract and Discussion, page 2068-9. Claims 3-4 are anticipated by Hughes et al as the aggregate-prone protein comprises β-amyloid chimeric proteins (LexA-Aβ fusion and B42-Aβ fusion, see Experimental Procedures). Claims 6-7 are anticipated as the chimeric protein comprises at least an aggregate forming domain of a mammalian amyloid polypeptide, operably attached to a detectable marker protein. Claims 12-13 are anticipated as the amyloid polypeptide is β-amyloid and comprises at least about amino acids 1-42 . Claims 17-18 are anticipated as the aggregate is labeled with a chromophore (ECL

detection, see Experimental procedures). Thus, claims 1, 3-4, 6-7, 12-13 and 17-18 are anticipated by Hughes et al.

***Status of Claims***

19. No claims are allowed.

20. Any inquiry of a general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for Group 1600 is (703) 308-4242.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sharon L. Turner, Ph.D. whose telephone number is (703) 308-0056. The examiner can normally be reached on Monday-Friday from 8:00 AM to 4:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached at (703) 308-3995.

Sharon L. Turner, Ph.D.
July 29, 1999

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